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THE RESEARCH BACKGROUND OF A SYSTEM OF NEUROENDOCRINOLOGIC FORMULATIONS*

PART I
OF
PHYSIODYNAMICS AND SOME MAJOR METABOLIC DISORDERS

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For the past five years observations have been gathered, experiments defined and data correlated by our group in an endeavor better to comprehend the pathophysiology of certain psychiatric processes. A few of these have been reported, some are in press, but most are still in manuscript and in protocol. Outlines of an emerging pattern, however, permit of tentative formulations of pathogenetic mechanisms in some psychiatric disorders.[1] These are based on our own work and on data reported by other investigators. This report attempts to integrate a complex picture within a comprehensive theoretical frame of reference. It may help better to focus some findings previously confusing or conflicting. It is presented for that critical evaluation and testing which can contribute much to clarity of thought and research planning.

To appreciate the origins of this material, it may be well to retrace some of the pathways along which our thinking and our work have progressed.

Parts I and II of this series relate to the schizophrenic, involutional and manic-depressive psychoses, the psychoneuroses as a group and the psychosomatic disorders. Subsequent communications will present and develop the dynamic formulations in both psychiatric and non-psychiatric disorders.

*Appreciation is expressed to Dr. Frederick MacCurdy, Commissioner of the Department of Mental Hygiene, State of New York, for his warm encouragement; to Dr. H. A. LaBurt, Senior Director, Creedmoor State Hospital, for his support and assistance and to Dr. Marvin Weinberg for his valued suggestions on the biochemical aspects of this report. Thanks are given to other members of the staff: to Dr. Felix Marti-Ibanez and Dr. Sydney S. Lazarus for their critical comment on the manuscript; to David Greenberg for his work on some of the technical details relating to the manuscript; and to Mrs. Florence Levin and Miss Imie Lane for their untiring efforts in preparing the manuscript for publication.

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PART I

Our early clinical observations first related some features of the psychoses to such familiar and physiologically understandable conditions as the recognized anoxias. Mental symptoms occur both in the anoxic anoxia of high altitude flying and in the anoxic and histotoxic (fundamentally "metabolic") anoxia of second stage anaesthesia. In both there is a primary interference with the delivery of adequate oxygen to the neurone. In severe B-avitaminosis, however, the psychic symptomatology may express an intrinsic metabolic anoxia fundamentally related to disruption of the neurone enzyme systems involved in carbohydrate metabolism. These considerations suggested that interference with neuronal oxidative processes could have a different and/or multiple origins. The futility of administering oxygen to psychotics became evident with the realization that even the highest blood oxygen tensions, per se, could assure neither the ultimate delivery of adequate oxygen to the neurone in anoxia due to a cerebral vascular impediment, nor its proper utilization within the neurone in metabolic anoxia. Could changes in the oxidative processes in the neurone be responsible for the benefits of electroconvulsive therapy (ECT)? If so, were these changes brought about through some influence on the vascular muscle coats and/or alterations in capillary permeability in the brain, over and beyond its possible direct effects on the pituitary gland and the neurone?

ECT, Histamine and Mental Disease

An electric current as used in ECT, administered to one ear of a rabbit was found to produce a moment of blanching followed by vascular dilatation. Then, after an interval of less than a minute, the vascular bed of the contralateral ear became dilated. There was a marked alternation[2] between vascular constriction and dilatation. Could it be that a blood-borne H substance, perhaps histamine, was being liberated? Accordingly, it was desirable to explore the possibility that ECT was achieving beneficial effects through "histamine" liberation with consequent cerebral vasodilatation and improved cerebral neurone metabolism. Because of technical limitations, bioassay for histamine was deemed impractical and indirect evidence via gastric secretory effects was sought.

As a base-line study, analysis of fasting gastric hydrochloric acid secretion in more than 100 psychotic patients was undertaken. It revealed a greater degree of fasting achlorhydria and hypochlorhydria than has been recorded in "normals".[3] Seven

[2] The phasic character of this change was encountered later in other phenomena.

[3] The importance of these findings in regard to vitamin B and C absorption was noted. Later their endocrinologic significance was to be correlated with other data.

patients were then studied for 60 days to determine the influence of ECT on fasting gastric free hydrochloric acid. Immediate stimulation of acid free secretion by ECT was demonstrated,[4] a phenomenon which could result either from "histamine" liberation or from vagal stimulation. The first possibility led to the administration of histamine in order to determine its effect on psychiatric disorders and for comparison of its effects with those of ECT.

Histamine Biochemotherapy of Hospitalized Psychotics

Thirty-eight patients with schizophrenic, manic-depressive and involutional psychoses were given histamine parenterally. The convalescent status rate following the use of this non-convulsive procedure was comparable to that attained by a control series receiving ECT. The response to histamine was characterized, moreover, by greater mental clarity, in contrast to the confusion common following convulsive therapy. The histamine-refractory patients, some of whom had been ECT-refractory previously, were then given ECT. These histamine-pretreated patients achieved benefits comparable to the ECT control group. Histamine used alone and, when necessary, followed by ECT, doubled the number of patients showing improvement and of those attaining convalescent status, even as it spared half of the latter ECT.

It is interesting to note that other workers, in demonstrating the liberation of histamine in insulin coma therapy, have related the depth of insulin coma to the height of the blood histamine level rather than to the depth of the hypoglycemia. Recognition that histamine may be involved in both insulin and electro-convulsive therapies, however, did not exclude the possibility that these therapies could, at the same time, be operating through other mechanisms as well—indirectly through the pituitary-adrenal-gonadal interrelationships and directly upon neuronal metabolic processes.

At about this time, our hypothesis of the phylogenetic evolution of the etiology of certain mental disorders was formulated. The postulate, briefly stated, was that the evolution of man's endocrine defenses too often fails to keep pace with the environmental changes wrought by the technical revolutions and the developing social forces of our civilization. Thus, an archaic physiology mobilizes—via the adrenals—to meet current emotional and intellectual emergencies on the muscular and metabolic plane of fight or flight. In an appreciable segment of our population—the psychotics—such an anachronistic form of mobiliza-

[4]Here an interesting rhythmic or phasic pattern of secretion over several days was noted.

tion persists despite the fact that most current stress situations demand cerebral rather than musculoskeletal means of defense. This disparity between demand and physiologic response could conceivably lead to impairment of cerebral neurone metabolism with attendant psychopathology. In situations in which the response to stress is one of excessive adrenal output, [AdH+], leading to deranged metabolism, histamine may act as a biochemotherapeutic agent intervening favorably in the undesirable sequence of events (1) by increasing cerebral blood flow and/or (2) by possible effects upon the pituitary-adrenal-gonadal interrelationships.

Consistent with the possibility of such over-reacting adrenal response. which if uncompensated may be termed relative [AdH+] dysequilibrium,[5] are both the low incidence of allergies and peptic ulcer (which may be referred to as relative [H+] or [AdH−] dysequilibria). and the high frequency of hirsutism and hypochlorhydria in psychotic patients. A further support is the observation that in those few psychotic patients in whom psychosomatic disorders occur, the latter tend to improve during acute psychotic episodes.

A SERIES OF DIVERSE DEVELOPMENTS

Chance then made a series of contributions.

A. *The Weather:* The response of psychotics to weather changes became an intriguing element in the complex puzzle. Patients seemed to act as physiological barometers anticipating atmospheric storms. A review revealed that the incidence of suicides had been statistically correlated with atmospheric pressure changes. To this was added the incidental observations of workers in a very active morgue, that at the time of suicide, a high percentage of these women had been menstruating. The temptation to relate cerebral dysfunction to a fall in atmospheric pressure was as appealing as the simple theory that an acute drop in estrogen-progesterone levels disrupts neuronal function.

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[5]It is imperative to state, at this point, that we must perforce oversimplify many aspects of the endocrinology and physiochemistry into which we venture. For example, adrenal output is here, for the moment, referred to as [AdH] despite its gross differentiation into medulla and cortex. Later reference is made to adrenal cortical hormone [ACH], despite the extraction of some twenty-eight fractions from the cortex. In most of the discussion of the met bolic effects of the adrenal cortical hormones, these will be considered as one entity regardless of the realization that each of the isolated crystalline compounds functions somewhat differently, in some degree, in regard to a wide variety of metabolic activities (such as the handling of carbohydrates and the regulation of fluid and electrolyte balance). Reference will later be made to the "sex hormones" as gonadal hormones, [GH], (follicular, [G_EH], corpus luteal, [G_PH], testicular, [G_TH]), despite the fact that some of the cortical elements isolated are sex hormones (such as estrone and androsterone). Since the gonadal hormones appear to counterbalance metabolically certain of the adrenal cortical functions, the existence of intracortical hormonal equilibria would be implied by their elaboration in the cortex. At this time, these considerations seem to be beyond the realm of even theoretical discussion. The dysequilibria, which for convenience will often be referred to as [ACH+] dysequilibria, are, more precisely, dysequilibria dominated or characterized by adrenal cortical excess.

Full acceptance of such interpretation was tempered by recognition that the degree of *direct* influence of both factors might be slight. The possibility of endocrine mediation, particularly adrenal, with consequent effects on cerebral vascular supply, electrolyte and fluid balance, and even more directly on neuronal metabolism, was only later to assume significance in the development of our formulations.

B. *Artificial Hibernation:* The experience of one of our group with the use of prolonged sleep therapy interested us in the effects of artificial hibernation on psychotics. It was found that it had been tried with disastrous results, the fatalities causing the investigators to react vehemently against the procedure. Yet this finding in itself was valuable, for when correlated with reports on the temperature-regulating mechanisms of schizophrenics, it further focused attention on the well-known loss in resiliency of body equilibria in this disease.

C. *Peripheral Vascular Collapse:* During our early studies with histamine, peripheral vascular collapse interrupted an intravenous infusion of histamine. Circulatory recovery followed administration of adrenal cortical hormones, epinephrine and oxygen. Collapse recurred within fifteen minutes and responded to similar management only to recur once more. Circulatory recovery following treatment of the second relapse was sustained. This incident suggested that a form of physiologic "neutralization" might have been taking place. It was as if histamine was counter-balanced by therapeutic agents whose quantities were sufficient in the first place only to "bind" the histamine in the blood stream; and then, it seemed as though vascular collapse recurred as additional histamine reappeared in the circulation, perhaps, from the extra-vascular compartments. This continued until all the histamine which had been administered was "countered" by adequate quantities of therapeutic antagonists. The evaluation of such a chain of events, therefore, necessitates not only consideration of the characteristics of the reactants, but constant interpolation of the factors of time patterning and concentration as they relate to the reactants.

Accordingly, it was thought that some observations on the minimum lethal dose of histamine in dogs could be an important basis for the further study of the role of histamine in body economy.

D. *The Pregnant Bitch:* At that time, attention was called to a report that methenamine had anti-histaminic effects. In the course of checking this report, the phenomenon of repeated clotting in the femoral arteries of a dog made it necessary to sacrifice the animal. It was decided to accomplish this by the use of a lethal dose of histamine. Seven hours later that dog, weighing 2.3 Kgm., had survived 96 mg. of histamine base

(278 mg. of histamine acid phosphate), with as much as 18 mg. of the base given in a single intravenous injection. In the search for an explanation, examination revealed the bitch to be pregnant.

Gravidity had apparently conferred remarkable resistance to histamine. This experience led us, some four years ago, to relate the improvement, during pregnancy, of such disorders as asthma, hay fever (and other allergic phenomena), peptic ulcer (and other psychosomatic disorders) and arthritis to a high titre of physiologic substances characterized by potent histaminolytic effects. Our formulations then suggested that there is psychiatric as well as metabolic significance in the observation that in pregnancy, as in the psychoses, large amounts of powerful histaminolytic substance or substances are probably elaborated. Corroboratively, the literature at that time contained a Roumanian and a German report on the finding of high histaminolytic titres during pregnancy. A Swedish investigator recorded this increase to be as much as a thousandfold. The substances which are elaborated during pregnancy and have dramatic effects in allergic and psychosomatic disorders were thought by us to be steroids—adrenal and, perhaps, placental in origin. These considerations led to the possibility of the use of a diagnostic skin test for states characterized by high antihistamine titres. This procedure of skin assay was applied in attempts to evaluate the histaminolytic levels of psychotic and psychoneurotic patients.

E *Twelve Puerperal Psychotics:* The fortunate coincidence of having twelve puerperal psychotics gather in our pavilion at this time gave further form to the hypothesis that marked shifts in endocrine output, abrupt or protracted, might be involved in the etiology and pathogenesis of certain psychoses For, here were seen twelve women whose histories showed, at the very least, a chronologic relationship between sudden alterations in hormonal equilibria and the onset of a psychosis Could restoration of the endocrine levels of pregnancy reverse the physiopathology? This study could not be pursued then to a conclusive stage because of unavailability of sufficient quantities of requisite hormones However, the observations then made did serve as another example of the relationship between the return of menses, reflecting restoration of more normal hormonal equilibria, and a remission of the disease process [6] This enhanced the realization that gonadal hormone levels could be, in a real and very practical sense, major determinants of general endocrine activity and particularly of adrenal hormone effects These contributions to the evolving central concept encouraged our continuing investigations into the influences of steroids in high dosage and of

[6] Which was cause and which was effect could not then be demonstrated either in the patients receiving estrogen and progesterone replacement therapy or in the control group.

histamine on adrenal hormone function and on the psychotic and other psychiatric processes

Histamine Studies in Non-Hospitalized Psychiatric Patients

The histamine studies were extended to non-hospitalized patients having various psychiatric disorders. Prompt and prominent was the finding of a striking difference in histamine tolerance between psychoneurotics and psychotics. Almost every psychotic had a relatively high tolerance to histamine while psychoneurotics and patients with psychosomatic disorders showed poor tolerance. In some psychotics, the high tolerance to histamine was followed ultimately by a decrease roughly paralleling clinical improvement. Despite their fundamental difference in histamine tolerance, a number of psychoneurotic patients receiving histamine demonstrated symptomatic improvement, particularly of depression, tension, and anxiety (in acute states). Observations of differences in skin flares, direct eosinophile counts and cardiovascular reactions produced by histamine administration, as well as its effects on carbohydrate metabolism, are still being integrated in an attempt to develop biological differential criteria, both diagnostic and prognostic, for these psychiatric disorders.

As will be seen our formulations of the role of hormonal dysequilibria in the etiology and pathogenesis of mental disorders, were thus considerably advanced particularly in respect to adrenal participation.

A. *Psychoses* vis a vis *Psychoneuroses:*

Here are two distinctly different types of psychiatric disorders related to each other by their diametrically opposed physiologic reactions to histamine.

1. Psychotics as a group generally tolerate enormous doses of histamine. In one patient, the unusual amount of 14 mg. of base (approximately 42 mg. of histamine acid phosphate) was given (in divided doses—7 mg. base at a time) within 35 minutes without peripheral vascular collapse.

2. Psychoneurotics as a group are relatively intolerant to histamine.

The theoretical implications of this may now be explored in order to evaluate the significance of the biologic findings.

1. Could this difference in histamine tolerance of psychotics and psychoneurotics be the reflection of a difference in adrenal and/or other endogenous antihistaminic activity? If adrenal, then one might postulate that the "functional" psychoses (schizophrenic, manic-depressive manic, involutional and puerperal) might be an expression of uncompensated [ACH+] dysequilibria. Psychoneuroses, in contradistinction, could express relative [ACH−] dysequilibria.

2. Can two different clinical processes, related (in these theoretical considerations) by two diametrically opposed pathogenetic mechanisms, respond favorably to a single form of therapy—in this case, histamine? The answer is that *some* patients in each diagnostic category did.

3. How reconcile the achievement of improvement in hypothetical relative [ACH+] dysequilibria with that in relative [ACH–] dysequilibria in response to the same therapeutic agent? Examination of this problem posed a number of alternatives:

(a) The difference in adrenal output and in adrenal reserve may predetermine its response to a given stimulus.

(1) Adrenals with low output and adequate reserve may respond to a given stimulus or substance with an increase in output. For example, if a psychoneurotic were in [ACH–] dysequilibria and his adrenal cortex responded to suitable stimulation, then alleviation of some symptoms might occur with the approach to [ACH] equilibria.

(2) Adrenals with high output and poor reserve (schizophrenia?) may respond to a given stimulus by an ultimate depression in adrenal function (as in insulin coma therapy) with resultant movement in the direction of [ACH] equilibria.

(b) Quantitative differences in the stimuli may bring about different responses in a given gland: A small amount of histamine may stimulate, and a large amount "exhaust", or depress, adrenal function. This is no more remarkable than the fact that the alkaloid nicotine in its direct action on ganglion cells first excites and then depresses them.

4. Are there grounds for the assumption that two different psychiatric disorders may develop as the result of diametrically opposed mediating processes which are set in motion by different concentrations of the same substance? Such grounds exist, but at this juncture it seems preferable to introduce consideration of another factor such as the hormone of the adrenal medulla, [AMH]. To illustrate, a psychoneurotic in relative [ACH–] dysequilibria could suffer periodically from cerebral neurone dysfunction because of such factors as cerebral vasoconstriction resulting from a relatively high output of medullary hormones, [AMH+] during acute episodes. In the schizophrenic, on the other hand, neurone dysfunction may follow (1) neuronal protein breakdown due to gluconeogenetic effects such as are typical of the 11-oxysteroids, (2) marked shifts in fluid balance due to the [ACH] alterations in electrolytes, and/or (3) possible chronic

effects of [ACH] on the permeability of the cerebral capillary bed and the dynamics of the vascular tree.

5. Can a single substance, histamine, produce symptomatic improvement in two different psychiatric disorders, one hypothetically presenting adrenal cortical dysequilibria [ACH+] and the other, adrenal medullary dysequilibria [AMH+]? In the psychoneuroses, episodes of anxiety, tension and depression are frequently alleviated by histamine administration. According to our formulations, this may be related, in part, to a counterbalancing of excessive medullary effects, [AMH+] by the histamine.[7] On the other hand, improvement in certain psychoses may generally accrue from the counterbalancing of [ACH+] dysequilibria, as well as from ultimate depression in output of an hyperactive cortex.

6. The assumption that cerebral function may be disturbed by these two mechanisms renders it imperative to examine how these might be related to the definitive differences in symptomatology of schizophrenia and psychoneurosis.

To speculate: (a) In the psychoneurotic, a transitory neurone anoxia may result from a relatively higher oxygen requirement and/or a deficiency in oxygen delivery due to [AMH+] effects on circulatory distribution. This may lead to neuronal disruption more functional than organic. Such dysfunction may be expressed as a disturbed response to reality and not a dissociation from it. On the other hand, (b) in a schizophrenic the progressive disruption and ultimately more malignant destruction of neuronal protein structure (through the chronic protein catabolizing effects of operative [ACH+] dysequilibria) may lead to depersonalization, withdrawal and progressive failure to comprehend reality stimuli. In effect, our formulations maintain that there is no such thing as a "functional psychosis"—the psychosis being a dysfunction resulting from micro-organic changes. In the psychoneuroses, on the other hand, the symptom picture may be primarily a reflection of neuronal dysfunction rather than organic destruction.

B. Psychosomatic Disorders

A number of patients with psychosomatic disorders (peptic ulcer, hay fever and asthma) were included in our histamine biochemotherapy studies. Some responded with an improvement in their ulcer, hay fever or asthma symptoms, which results did not necessarily correlate with changes in their psychiatric picture. If one were to postulate relative [ACH–] [AMH–] dysequilibria for these psychosomatic disorders, then how could one understand a somatic improvement in some of the patients receiving histamine treatment?

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[7]This does not exclude the possibility that in the psychoneurotics histamine may likewise be achieving some activation of adrenal cortices with low output and good reserve.

For some time now, it has been common practice to refer to peptic ulcer, asthma, hay fever and allergies as "histamine induced states" even though high histamine titres have not been directly and consistently demonstrated. One may, for theoretical purposes, equate relative [ACH–] [AMH–] dysequilibria with relative [H+] dysequilibria. Two alternate possibilities may then be considered:

1. An absolute increase in [H] titre may imply a failure of adrenal counterbalancing response.
   (a) If this failure be due to lack of cortical and medullary reserve then histamine therapy should not be expected to produce any beneficial effects; on the contrary, it should result in aggravation of symptoms.
   (b) However, if the failure be due to adrenal refractoriness to existing endogenous [H] levels despite the presence of cortical and medullary reserve, then increasing [H] levels by histamine administration might invoke adrenal activity, with resultant change in the equilibria toward compensated balance with symptomatic improvement.
2. On the other hand, the [H] may be normal, or (for that matter) even below normal, but the adrenal output very low, [ACH$^{=}$] [AMH$^{=}$], due either to poor adrenal function and/or poor adrenal reserve and/or a relative inadequacy of endogenous histamine levels. The relative [H+] or [ACH–] [AMH–] dysequilibria might then, depending on adrenal sensitivity and reserve, respond to histamine administration.

If relative [ACH–] dysequilibria be more closely examined, it becomes evident that they may be associated with disturbance in transcapillary glucose and oxygen movement. If such an interference occurs, then it may be equivalent to neuronal anoxia and/or disruption of glucose metabolism. It is therefore theoretically possible that psychiatric symptoms could occur in [ACH–] [AMH–] dysequilibria (psychosomatic disease?). The same interference could be basic to the cerebral dysfunction in [ACH–] [AMH+] dysequilibria (psychoneurosis?). In support of the postulate that interference with neuronal energy metabolism may cause cerebral dysfunction, may be cited findings of a full gamut of psychiatric symptoms in B vitamin deficiencies and their response to replacement vitamin therapy.

We have, therefore, noted that disruption in neuronal oxidative mechanisms can theoretically occur either (a) by the limitation of oxygen reaching the cell membrane, (b) by the impedance of passage of oxygen and glucose through capillary and neurone membranes, and (c) by interference with the glucose oxidative cycle: i.e., at 1,3—diphosphoglyceraldehyde in the

oxidative breakdown to 3 carbon sugars in the case of nicotinamide deficiency; and in the tricarboxylic acid cycle at isocitrate or pyruvate (in nicotinamide, thiamine and riboflavin deficiencies); at ketoglutarate (in thiamine deficiency); or, if the cycle in the brain differs from that in muscle, then the disruption could result from deficiencies of thiamine, riboflavin or the cytochrome systems at phosphohexonic acid. In any event, interference can also be postulated in the phosphorylation mechanism if the adenine-ribose complex be disrupted.

Studies of Steroids in the Psychoses

The effects of massive doses of sex steriods and some newly synthesized related compounds[8] have been observed in the psychoses. Of particular theoretical interest, especially in relation to the previous observations of puerperal psychoses were the prompt and dramatic responses of a number of psychotics in the involutional phase of life. In terms of our formulations, they could be considered as examples of relative $[G_{EP}H-]$ dysequilibria. Dynamically, in simple terms, they would, therefore. be in $\frac{[ACH+]}{[GH-]}$ dysequilibria. Involution of the ovaries may release one of the checks on the pituitary with consequent over-activity (in part [ACTH+]), and the development of both absolute and, perhaps, relative [ACH+] dysequilibria. Fortunately, this development is limited—probably to those women whose pituitary and adrenal glands either fail to involute synchronously with the ovaries or whose pituitary and/or adrenals may be overly-sensitive to gonadal release. Subsequent pituitary-adrenal involution could explain the ultimate spontaneous remission clinically characteristic of this condition. Could the factor of pituitary sensitivity explain the dramatic response of involutional melancholics to a very few electroconvulsive treatments?

In this connection, one must also take note of the high incidence of hirsutism even in normal women following the climacterium. Since this is probably an expression of the frequency of relative [ACH+] dysequilibria at this epoch of life, then why are there not more involutional psychotics? More on this subject later.

In the involutionals responding to massive estrogen-testosterone therapy, the response could be formulated in abbreviated and simplified reaction form as follows:

$$\frac{[ACH+]}{[GH-]} + [G_EH+] + [G_TH+] \longrightarrow \frac{[ACH+]}{[GH+]}$$

[8]We have found that one of these, an easily synthesized and readily available steroid, has, among its unsuspected properties, the ability to produce a few of the biochemical alterations characteristic of cortisone.

If this be so, then how explain the "paradox" that one form of schizophrenia (herein also postulated as [ACH+] dysequilibria) seems to be specifically related to puberty and adolescence? Clinically, the chronologic correlation is unquestionably valid, but it cannot be assumed that puberty, per se, in all individuals results in a sudden spurt in gonadal output. On the contrary, the gonads may be relatively refractory or inadequate and the adrenals relatively more responsive to a sudden increase in pituitary activity. It is precisely this fact that may explain the onset of adolescent schizophrenia at puberty. It is particularly significant that results as dramatic as those achieved in involutional psychotics, though more delayed in appearing, were attained in a few adolescent schizophrenics treated with massive estrogen-testosterone therapy. In interpreting this, the same equation may be formulated as above. Not only did the symptoms clear but also the patients literally grew up physically and emotionally in but a few weeks.

At this point, two additional considerations contribute toward rounding out the formulations.

1. If marked facial flushing reflects a similar cerebrovascular response, then cerebral vasodilatation may make a significant contribution to neuronal metabolism in steroid therapy, for, in practically all patients the flush phenomenon invariably characterized the early and the terminal tapering-off phase of the therapeutic course. Still more interesting from the theoretical standpoint of our formulations are:

2. The anabolic effects of the steroids. The well-known nitrogen retention associated with testosterone was manifested in our patients by marked increase in weight and improvement in muscle tone. It is not beyond the realm of possibility that in the neurone such anabolic effects could exert favorable influences on neuronal protein structure. These would counterbalance the catabolic effects of adrenal cortical hormone, even as it has been demonstrated in Cushing's disease.

In histamine and the gonadal steroids, as well as in such substances as thyroid, insulin, adrenal cortical hormone and malononitrile, medicine may have the positive opportunities for maintenance and restitution of neuronal metabolic processes and for support and reconstitution of neuronal protein structure so fundamental to normal cerebral function.

SUMMARY

The evolving pattern of a research effort has been traced from its beginnings at the possible role of cerebral anoxia in psychiatry to problems of oxygen carriage, energy metabolism and neuronal protein structure.

Animal experimentation first suggested "histamine" liberation in ECT. Studies of the effects of ECT on gastric hydrocholoric acid secretion supported this possibility inferentially, even as it led to the realization that passage, through the brain, of the electric current used in ECT, may affect pituitary and neurones directly and the adrenal-gonadal relationship indirectly. The demonstration of a high incidence of fasting hypochlorhydria in psychotics was later to be correlated with evidence intimating excessive adrenal participation in the pituitary-adrenal-gonadal hormone interrelationships.

Investigation of the effects of histamine administration to psychotics demonstrated the therapeutic value of this substance and lent corroboration to the evolving formulations relating hormonal dysequilibria to the etiology and pathogenesis of psychiatric processes. The therapeutic role of histamine per se, its implication in insulin coma therapy, as well as its possible involvement in ECT, posed the prospect that some common physiologic mechanisms might be involved in the different successful modalities of treatment while a number of kindred pathophysiologic mechanisms might be involved in etiology and pathogenesis.

At this point, a theory was postulated on the phylogenetic development of the endocrine mechanisms which could be responsible (particularly via the adrenals) for the disastrous psychic responses to stress stimuli in some individuals.

Diverse clinical and experimental observations added corroboration to the premises of the developing concepts: (1) a low incidence of allergy and peptic ulcer and a high incidence of hypochlorhydria and hirsutism in psychotics (2) the recognized and suggestive correlation of suicide rates with changes in barometric pressure (3) the counterbalancing relationship between adrenal hormones and histamine (4) the tremendous histaminolytic blood titres of pregnancy which not only pointed to a possible mechanism for the improvement of certain somatic states but also intimated the possible etiologic role of (5) the endocrine dysequilibria in puerperal, involutional and pubertal psychoses.

Further investigation of histamine effects in psychoneuroses, psychosomatic disorders and early psychotic processes confirmed its therapeutic efficacy and brought to light the highly significant difference in physiologic response to histamine between the benign and the malignant psychiatric disorders. From the cumulative data, the outlines of a pattern emerged suggesting adrenal cortical excess ([ACH+] dysequilibria) in relation to gonadal and other hormones, as an etiologic and pathogenetic mechanism in certain psychoses and a relative adrenal deficiency ([ACH–] dysequilibria) in relation to other hormones as a factor

in the psychoneuroses and the psychosomatic disorders. Data relevant to both psychoneurotic and psychosomatic disorders also implicated the medullary hormones in the intricate pattern of hormonal dysequilibria. The findings foreshadowed possibilities for biochemical diagnostic and prognostic criteria and pointed to the significance of the metabolic effects of endocrines on neuronal energy metabolism and protein structure. These concepts help to bring into focus recent reports on damage of neuronal structure in malignant psychiatric processes.

In the investigation of sex hormones and other steroids the outstanding improvement of some adolescent and involutional psychotics gave confirmation to the formulations in regard to the role of the gonadal hormones in the psychiatric hormonal dysequilibria and helped clarify the prognostic implications of certain diagnoses. It also indicated that the anabolic effects of sex steroids may counter adrenal cortical catabolic effects on neuronal protein structure.

This report has thus traced the evolution of a number of elements of a theoretical formulation out of a highly ramified pattern of clinical and experimental psychiatric investigation.

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A SYSTEM OF PHYSIODYNAMICS AND ITS APPLICATION TO THE NEUROENDOCRINOLOGY OF PSYCHIATRY*

PART II

OF

PHYSIODYNAMICS AND SOME MAJOR METABOLIC DISORDERS

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The authors gratefully acknowledge the collaboration of Dr. Co Tui and his wholehearted contribution of time and effort, of penetrating insight, critical judgment and wisdom.

Significant hormonal patterns in varied psychiatric disorders have been noted in a series of clinical and experimental investigations (Part I)[1]. Research in the biologic effects of histamine, of electroconvulsive and sub-coma insulin therapies and of sex hormones and other steroids implicated not only the function of adrenal (cortical and medullary) hormones but also the secretions of the thyroid, pituitary, pancreatic islets and gonads in a complex of interrelationships which have been described as equilibria and dysequilibria of various types. The evolving patterns suggested common denominators in the etiology and pathogenesis of certain cerebral dysfunctions and the mechanisms involved were related to neuronal metabolism. The resultant formulations offered theoretical clarification of physiopathologic processes and presented biochemotherapeutic opportunities.

The formulations together with a number of seemingly unrelated and even contradictory psychiatric observations have been examined in the light of basic biologic principles. Some of these fundamental concepts, restated and supplemented, have been integrated into a system termed physiodynamics (Part II). Physiodynamic analysis enabled further development of the

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[1]Parts I and II relate to the schizophrenic, involutional and manic-depressive psychoses, the psychoneuroses as a group, and the psychosomatic disorders. Subsequent communications will relate the dynamic formulations to both psychiatric and non-psychiatric disorders.

neuroendocrinologic postulates. It led to an encompassing biochemical frame of reference for our psychiatric observations. The concepts of physiodynamics are not all our own; a few have been proposed by isolated workers, many have engaged the attention of different research groups, most are basic to the sciences. However, we cannot, nor would we wish to disavow our responsibility for a number of the newer concepts, for the manner in which older ones have been restressed and correlated, as well as for the integrating formulations and "formulae" presented herewith, albeit they are both preliminary and tentative.

PART II

ORIGINS AND DEVELOPMENT OF THE FORMULATIONS

Our earliest concepts originated in clinical observations. These led to experimental activities out of which much of the structure of the formulations grew. Later, consideration of a number of critical clinical questions helped to put "meat on the bones". Here are a few of the clinical "whys" and "hows" which served as important points of departure in exploring and elaborating our hypotheses.

Why the prognostic difference between the schizophrenic and manic-depressive psychoses?

How explain the regression, "scarring" and ultimate deterioration in schizophrenia and the immunity of the personality in the manic-depressive psychosis?

Why the good prognosis for spontaneous remission in most psychoses first occurring puerperally or during the climacterium?

How account for spontaneous remissions in some schizophrenics?

Why the relatively easy therapeutic reversibility in most cases of involutional psychosis?

How can seemingly comparable circumstances cause a psychosomatic disorder in one individual and not in another?

Why are the same physiologic events (pregnancy and parturition) followed by a psychosis in one person and a post-partum asthenia and/or depression in another?

How account for the difference in histamine tolerance between psychoneurotics and psychotics?

What do psychoses occurring at puberty, post-puerperally and during the involutional phase of life have in common?

Do factors of heredity play *the* dominant role in the etiology of schizophrenia?

Can the schizophrenic process be initiated or reproduced biochemically?

The search for answers to such questions and the reconsideration and integration of experimental and clinical data have led

to the further development of our theses. Fundamental to our formulations are those common factors which are constantly exerting an influence in the etiology, pathogenesis and progress of common psychiatric processes: time patterns, hormonal concentrations and stress magnitudes; the interacting elements, the cortical hormones and their counterbalancing forces (antidynes), their manifestations in varying equilibria and dysequilibria and the tissues upon which these act.

Processes in Time

Biologic phenomena as well as their underlying chemical and physical processes become meaningless abstractions unless viewed in the dimension of time as well as the dimensions of space. The time-wise structuring or patterning—the manner of variation and the duration in time—of each variable in our formulations is itself an essential variable, influencing the biochemistry, its effects upon neuronal structure and function, and through these, ultimately, the symptomatology and prognosis of every psychiatric process.

For purposes of analysis, the patterns of a process in time could arbitrarily be classified as "continuous" (or unremitting or unrelenting), as phasic, and as episodic.

Time Patterns: The outstanding characteristic of schizophrenia in time patterning is its relative "continuity". The patient appears to be subjected to forces which are "unrelenting". The disorder is chronic and progressive. As each repeated exacerbation abates, it practically always leaves the patient with further "scarring". Even in remissions, the schizophrenic remains a schizophrenic. A relatively "unrelenting" time pattern may well of itself be of decisive importance. In the biochemical terms of our formulations, persistent or persistently recurring hormonal dysequilibria characterized by adrenal cortical excess as related to the neurone,[2] and its unrelenting cata-

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[2]This has been previously discussed in Part I as a probable etiologic and pathogenetic factor in a number of psychoses. For convenience it will later often be referred to as [ACH+ dysequilibria, or more precisely, dysequilibria dominated by adrenal cortical excess, [ACH+]. For easier reference in the theoretical presentation, a glossary of the abbreviations proposed in Part I is included:

Endocrine Glands

[Ad]	— adrenal	[P]	— pituitary
[G]	— gonad	[Th]	— thyroid
[Is]	— pancreatic islets		

Hormones

[ACH]	— adrenal cortical	[H]	— histamine	[InH]	— insulin
[AMH]	— adrenal medullary	[G_PH]	— progesterone	[ThH]	— thyroid
[G_EH]	— estrogenic	[G_TH]	— testosterone		

Dysequilibria dominated by:

[ACH+] — operative adrenal cortical excess related to the neurone—schizophrenia, manic-depressive manic and involutional psychoses.

[ACH−] [AMH−] — operative adrenal cortical and medullary deficiency relative to the neurone or other specific end-organ—some phases of psychoneuroses and psychosomatic disorders.

[ACH−] [AMH+] — operative adrenal cortical deficiency and adrenal medullary excess,

bolic effects on neuronal protein and other disruptive effects on neuronal metabolic processes, afford the neurone less and less opportunity for reconstitution. Clinically, regression is followed by deterioration which, though more readily reversible in its early stages, seems to become progressively more irreversible as the organic changes continue. The relatively "continuous" time patterning of schizophrenia is common to most of the simple, the hebephrenic and many of the catatonic schizophrenics. A progressive time pattern with arrest at a point in time seems to characterize some paranoid schizophrenics. Deterioration is seemingly limited or considerably slowed, but damage may be such that psychopathology continues to manifest itself. Intermittent episodes characterize most catatonic schizophrenics. In these, "scarring" appears to be more limited and adjustment during remissions better than in the more unremitting time patterns.

In contrast to the relatively "continuous" process of schizophrenia is the more obviously phasic or cyclic clinical course of the manic-depressive psychosis. The difference in time patterning of the postulated biochemical dysequilibria may be reflected in the fact that neurone pathology and consequently personality deterioration are limited—"scarring" is absent. The time patterning of this process permits reconstitution of disrupted neuronal structure and restitution of more normal metabolic processes during its frequent and often prolonged, free intervals.

Episodic time patterns are typical of puerperal and involutional psychoses, of reactive depressions and of the combat and traumatic neuroses.

Extent of a Process in Time: Total duration must be considered in the evaluation of every disease process and therapy. The more favorable response to therapy of psychiatric processes of short duration emphasizes the need for the earliest possible diagnosis and the earliest possible treatment. The total extent of a process in time may be a major determinant of the degree of neurone pathology in those disorders in which the underlying biochemical process affects the basic protein structure of the neurone. Significant is the well-known "change in diagnosis" after the passage of time. Such change, when made, is almost invariably to schizophrenia, rarely from schizophrenia to manic-depressive or other psychosis. These considerations may indicate

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relative to the neurone—some phases of the psychoneuroses e.g., anxiety state and manic-depressive depressed psychosis.

[H+] — relative histamine excess—psychosomatic disorders

These are, in effect, abbreviations for the very complex dysequilibria—for, a preponderance of ACH may reflect an absolute and/or a relative increase or decrease in concentration of this hormone as it relates to its counterbalancing hormones, viz. estrogens, progesterone testosterone, thyroid, insulin and histamine.

why, in the psychoses, prognosis is so much a function of the duration of the process.

Point in Time: The most critical point in time, in a psychosis such as schizophrenia, is that hypothetical juncture (nodal point) at which organic change within a neurone becomes irreversible. Thus, it is apparent that therapies which shorten an episode are, despite other shortcomings, major therapeutic contributions. The prompt abortion or limitation of psychotic episodes, in the course of a patient's life, may be *the* determinant in preventing or limiting irreversible organic damage and deterioration, since the malignancy of an abnormal process is an expression of its irreversibility, which, in turn, can be the result of its persistence and total duration.

Attempts to interpret biochemical findings and therapeutic responses in different patients with schizophrenia can be very baffling, until one appreciates the significance of the "point in time" at which the observations are made. Evaluation of biochemical observations and therapeutic responses, without reference to the duration (and the severity) of the processes under study, can be misleading. That this problem does not lend itself to an easy solution is readily apparent to anyone who has attempted to categorize patients under investigation according to these criteria (duration and severity). Though we must await further biochemical developments to define more precisely the developmental stage of a psychiatric disorder, nonetheless, consideration must constantly be given to that point in time at which data are collected and the process is analyzed.

Concentration or Magnitude of Interacting Elements

Essential to the evaluation of any substance or force acting on or within the body is its concentration or magnitude.[3] Here again, gross quantitative differences may express themselves in different clinical terms. The almost total loss of adrenal cortical output resulting from cortical destruction produces [ACH≡] dysequilibria manifested in the classic picture of Addison's disease. Less marked reduction in cortical output may result in [ACH−] dysequilibria, in relation to such end-organs as lungs or stomach, making itself manifest (according to our formulations) in a psychosomatic disorder, viz., asthma or peptic ulcer. These examples are, of course, oversimplifications. In the complexity of body dynamics, the concentration or magnitude of any substance or force may have three different expressions: absolute, relative and operative.

1. The absolute concentration or magnitude of any substance or force is a primary attribute but, by itself, does not determine its effects within the body. For example,

[3]These are symbolized by the chemical convention [ ].

pregnancy is characterized by a marked increase in the absolute concentration of many endocrine factors; among these, estrogen [G_EH+], progesterone, [G_PH+], and adrenal cortical hormones [ACH+]. Yet, it is normally not disturbed by symptoms of hyperestrinism or excessive adrenal cortical activity. In effect, the high absolute concentrations of these elements exist in what may be termed compensated equilibria—that is, one in which the effects of the high absolute concentration of any one are balanced out by proportionate increases in the concentration of factors with opposing or counterbalancing actions to which we later refer as antidynes.

2. Relative concentration or magnitude is physiologically more significant than the absolute. It is the expression of the difference, or the ratio, between the substance being considered and its counterbalancing or metabolic opposites within the body. For example: a quantity of histamine administered to one patient—a schizophrenic —may produce practically negligible effects, while the same quantity given to a psychoneurotic may cause a severe peripheral vascular collapse. The absolute concentration of histamine administered may be the same for both, the physiologically active concentration, however, is its relative magnitude. In terms of the developing formulation; the psychotic, following administration of histamine, may in effect be in compensated [ACH+] equilibria; i.e., $\frac{[ACH+]\,[AMH+]}{[H^{+}_{+}]}$. The neurotic when receiving an equal amount, is forced into dysequilibria due to the excess [H^{+}_{+}]. This could be formulated as: $\frac{[ACH-]\,[AMH+]}{[H^{+}_{+}]}$; such dysequilibria may eventuate in peripheral vascular collapse.
3. Operative concentration or magnitude is physiologically the most significant aspect of any force. It is not an expression of concentration alone but is the magnitude of the effect produced by this force acting upon a specific end-organ. Thus, it is as much dependent on the sensitivity and responsiveness of the specific end-organ acted upon as it is upon the relative concentration of the force. The most frequent end-organs under consideration are the cerebral neurones and the endocrine organs; less frequently, the lungs, stomach, skin and musculature.

   The operative concentration is also in part determined by the metabolic requirement of the end-organ for the effector substance. If the requirement is high negative dysequilibria relevant to the organ tissue may exist, even with concentrations of the substances, which

would at other times be adequate; if the requirement is low, then operative dysequilibria may more readily develop in relation to that particular tissue.

In normal pregnancy, some women may be considered to present compensated endocrinological equilibria. However, seemingly normal pregnancy may cover ominous latent developments. For present purposes, consideration is limited to adrenal and sex steriod levels, and is further restricted to analysis of just two situations: (a) psychosis precipitated by parturition and (b) post-partum asthenia and/or depression.

(a) A woman with responsive adrenal cortices with both high output and high reserve who shows compensated [ACH+] equilibria prior to conception, may continue so during pregnancy on a still higher plane with absolute [ACH‡‡]. Endocrinologically. the second and third trimesters are marked by the dominant contribution of the placenta in the maintenance of the blood sex steroid levels. If, following delivery of the placenta, the adrenal cortices fail to reduce their output synchronously with the fall in sex steroid levels, then operative [ACH+] dysequilibria may result with consequent neuronal damage and development of a post-partum psychosis.

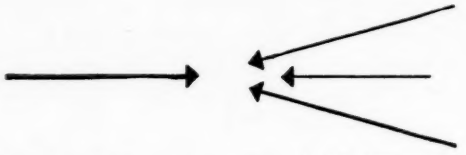
(b) A woman with relatively unresponsive adrenal cortices, who manages to maintain compensation during pregnancy, can develop [ACH-] dysequilibria during the puerperium. This may follow removal of the extremely high pituitary output during gravidity, particularly if, in conjunction, a high ovarian output is re-established early post-partum. This may express itself in an asthenia and/or depression.

Antidynes

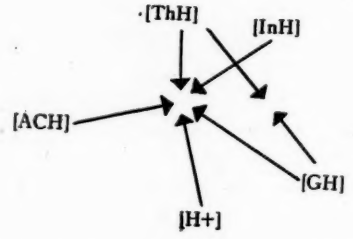
A fundamental physiodynamic postulate is the premise that the existence of any endogenous factor which can move a body function or biochemical action in one direction presumes the existence within the organism of one or several counter-factors, here termed antidynes, which can reverse the direction of the body function or reaction. This fact that any biologic parameter, at any given point in time, is in opposition to another, is well illustrated by the interaction of insulin, sex steriods, pituitary and adrenal hormones and the contributions of the liver, kidneys and muscle in the maintenance of blood sugar equilibria. Thus, the blood sugar level. at any one point in time, expresses the function of several counteracting elements and systems in relationship to each other at that point in time. Constant considera-

tion of antidynes will help prevent the distorted perspectives which so commonly ensue when one aspect of glandular function is isolated for study without simultaneous regard for the multiple elements, organs and systems intrinsically involved in the function singled out for investigation. In effect, *the physiodynamic approach recognizes that all biologic parameters and equilibria are expressions of the operations of opposites in body function.*

On the Actions of Antidynes: Hormones, individual organs (e.g., kidney, liver) and entire body systems (e.g., the nervous system) are constant participants as antidynes in many equilibria. For any one essential factor, therefore, multiple antidynes, each making a contribution of a different magnitude, may be anticipated.



For example: the antidynes, to any one adrenal cortical hormone, may be, in part, gonadal hormones, thyroid and insulin; in part, histamine; and in some situations, even sex steroids secreted by the cortex itself. Graphically, the interrelated counterbalancing actions may be simplified thus:



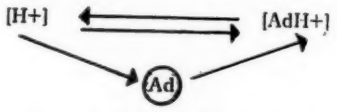
In different patients, the magnitude of the different vectors will differ and they may also differ within the same patient at different times. For example: [ACH+] dysequilibria in one schizophrenic may be marked by a predominant deficiency and/or excessive counterbalancing of thyroid—the patient may thus be able to tolerate enormous quantities of thyroid. In another, gonadal "inadequacy" may be prominent and may manifest itself in amenorrhea. In a third, there may not be a predominating deficiency of any one antidyne, but of several. It is probably the rare patient in whom a single element is involved.

Counteraction of antidynes probably takes place at several different points or levels:

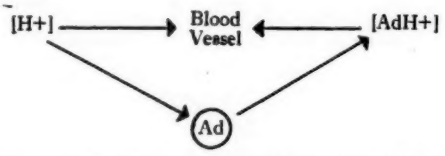
Direct chemical buffering, as in the maintenance of the *p*H

of body fluids, probably exemplifies the simplest of antidyne actions.

Indirect antidyne effects via a mediating organ may be the more subtle physiologic counterbalance used in maintenance of hormonal equilibria. For example: histamine in slightly excessive amounts may stimulate adrenal activity and, thereby, counterbalance its own physiologic effects:



Indirect antidyne counterbalance at an end-organ may be one of the common "neutralizing" mechanisms. For example: the histamine may not be chemically "neutralized" but balanced out in a vessel wall:



For purposes of further exploration, let it be assumed that [ACH+] dysequilibria develop in certain patients at puberty, in pregnancy or during involution. Failure of the gonads to respond, or the sudden removal of gonadal hormone concentration, may then lead to the appearance of psychiatric symptoms. These dysequilibria may be corrected by the administration of gonadal hormones, as we have done, therapeutically. Does the therapeutic procedure operate only through the re-establishment of the gonadal check on the pituitary and/or the adrenal cortex? We must here consider the possibility of some form of end-organ antidyne effect. For example: the administration of histamine, or of gonadal steroids, may not only act via the pituitary and/or the adrenal glands, but it also may counter the effects of the cortical hormones themselves at the end-organ.

Such counterbalancing by antidyne effects at end-organs may be described from one of our studies. Thirteen female hospitalized psychotics received between 2,750 mg. and 4,625 mg. of testosterone propionate over a period of 30 to 42 days, without producing the masculinizing effects reported in women receiving between 400 and 500 mg. of testosterone a month. Each 100 mg. of testosterone propionate was balanced by the use of 3.33 mg. of estradiol benzoate—one of its antidynes.

The probable existence of mechanisms for counterbalancing the masculinizing effects of androgens is suggested by the fact that non-hospitalized psychotics manifested masculinizing effects with as little as 1,500 mg. of testosterone propionate, balanced

as above with estradiol benzoate. While balances between androgens and estrogens have long been known and appreciated, it must similarly be recognized that determinations of adrenal cortical output may have but limited significance if such are not constantly related to gonadal, thyroid, insulin, possibly histamine and other endocrine titres. In actuality, the effects of [ACH] on neurone structure are related in greatest measure to its operative concentrations; *vis a vis* the neurone—its effects are the function of:

$$\frac{[ACH]}{[G_{E,A,P}H] + [xH] + [yH] + [zH] + \text{other mechanisms}}$$

wherein, [x] may be thyroid, [Th], [y] may be insulin, [In], and [z], other endocrine factors.

HISTAMINE, A HORMONE

The theory of antidynes should, accordingly, lead to recognition of the existence of essential physiologic substances at present unknown or considered abnormal by-products—just as the chemist and physicist could hypothetically assume the existence of unknowns in the table of elements. As a case in point, one may postulate the existence of a number of substances or forces as essential physiologic agents, indispensable as antidynes for many of the cardiovascular, secretory and other functions of the adrenal cortical and medullary hormones. Histamine, or an H-like substance, seems well suited for such antidyne function together with other known physiologic substances.

Entering the blood stream directly from white blood cells and probably from every tissue in the body, histamine or the "H" substance is blood-borne to fulfill its hormonal mission. It may participate in the regulation of gastric secretion, in the maintenance of blood pressure equilibria, in the shifting of blood distribution to various regions, in the stimulation and counterbalancing of both adrenal medullary and cortical functions and, through their hormones, it may be involved in the control of protein catabolism, electrolyte and fluid balance. Indirectly and directly, histamine or an "H" substance may also be implicated in the regulation of capillary permeability. In fact, it appears to be able to exert an influence on practically every aspect of cellular metabolism through its ramifying actions and interactions with other hormones.

From the ubiquity of its sources, from the speed of its effects, from the promptness with which it is counterbalanced, one would be tempted to ascribe to it a vital role in the body's essential functions. Disruptions in its equilibria with its multiple antidyne elements may be expressed in a wide range of metabolic disturbances. In the event of relatively excessive [H+] dysequilibria, it may well make a contribution to the etiology

and development of such psychosomatic disorders as peptic ulcer, hay fever, asthma and others; as well as to the pathogenesis of the psychoneuroses. In relative deficiency dysequilibria, it may partake in the etiologic mechanisms of the psychoses and other metabolic disorders.

Equilibria

It is evident that in an organism composed of a complex of systems of innumerable, dynamically-counterbalancing elements, the function of each endocrine gland must be integrated within the total complex. In current dynamic physiology, the hormonal and other mechanisms have been assigned the function of maintaining "homeostasis". Too often, "homeostatic" conveys the impression that the dynamism of the body is dedicated to the preservation of uniformity or stability—a fixed "dead level" of function. The development of the dynamic concept thus carries, within its own phraseology and thinking, an element of "stasis". Comprehension of the physiodynamics of the body is better served by the less frequently used term of "dynamic equilibria."

Physiodynamics are better understood if it is recognized that the fluctuating equilibria of the organism function within a constantly changing range. For purposes of simplification, the range of equilibria may be visualized as being defined by an upper extreme level of equilibria and a lower extreme level of equilibria, with the upper and lower levels constantly shifting.

The expressions equilibria and dysequilibria have been selected advisedly. Body equilibria are in constant change and reference to any level or plane must of necessity refer collectively to the average of a number of equilibria, at different levels, for any one period of time. Reference has been made to the "continuous" or "unremitting" [ACH+] dysequilibria of schizophrenia. These are only relatively "continuous" for it is quite obvious that a schizophrenic cannot be in constant negative nitrogen balance. The "continuous" aspect of the dysequilibria is used to indicate that the variations of the equilibria are so closely spaced that they are "seemingly" or relatively "continuous". If one were to draw a connecting line between the upper levels of the equilibria, it might be represented somewhat as follows:

in distinction to the more phasic dysequilibria of the manic-depressive:

The rhythmic, cyclic or phasic aspect of body equilibria can be illustrated by: (1) the rhythmic pattern of flushing and blanching of the rabbit's ear and (2) the longer range rhythmic pattern in gastric secretion. These, taken in conjunction with the ovarian cycle and the diurnal secretion of adrenal cortical hormones, makes apparent the fact that patterns of equilibria ultimately must reflect the complex integration of the different rhythmicity of each of the implicated antidynes. This is significant both in considering pathogenesis and in developing therapeutic regimes.

At this point, one might venture a physiodynamic definition of "normal" function.

Normal function may be considered as the maintenance of body equilibria within those ranges in which the organism can best perpetuate the optimal continuity of its functions; those ranges of equilibria which best foster growth for higher development of function, defense for integrity of function and reproduction for further perpetuation of function.

Plane of Function: The range of equilibria, within which an organism functions, may be found at considerably different planes for different individuals or for the same individual at different times. In effect, the plane of function for compensated equilibria is determined by the absolute concentration of all factors and their antidynes. For example, in an oversimplification:

A woman may go through adolescence and adulthood with high adrenal cortical output [ACH‡‡] counterbalanced by a high gonadal titre [GH‡‡]. One might say that her functions take place in an elevated hormonal plane, with high absolute [ACH] and [GH] concentrations or one might term these very marked, but compensated [ACH+] or [GH+] equilibria: $\frac{[ACH‡‡]}{[GH‡‡]}$. In this instance, reactions to changes in gonadal hormone titres will, of course, differ considerably from those of a woman with a normal [ACH] output both at the time of menses and during the climacterium.

The withdrawal of the gonadal hormones with a compensating drop in adrenal function could, theoretically, give rise, during the first episodes, to some of the symptoms of pre-menstrual tension. Later in life, the biochemical trauma of marked dysequilibria, superimposed on prior neurone damage or acting on neurones sensitive to such injury, may eventuate in an involutional upheaval or a full-blown psychosis. In both, adequate restoration of such antidynes as the gonadal hormones should, and does, rectify the dysequilibria and also their effects, if damage is not irreversible.

The Interacting Elements

Examination of the interaction of various factors requires integration of the following: organ elements; stimuli, sensitivity and reactivity; organ capacity; susceptibility; environmental factors and their stress situations: psychic and physical.

The Organ Elements: Since a major determinant of the effects of any force is the structure upon which it acts, it becomes necessary to consider certain essential characteristics of the organism, particularly, the "mediating" endocrine and end-organ elements which are affected by the various forces.

The functional complexity of the dysequilibria under study obviously is influenced by the individual sensitivity of each of the organs and also by differences in their actual output, and their reserve or potential output. Every organ has the alternative possibilities of under-reacting, reacting normally or over-reacting. It may do any one of these in a different manner for different stimuli, and it may also react differently for the same stimuli at different points in time. Thus, quite a number of combinations or permutations are possible, even under a given set of environmental circumstances within which the structural and functional organ diatheses are disregarded.

The reactivity or non-reactivity of any organ is determined by the character and concentration of the stimuli, by organ sensitivity to the individual type of stimulus and by organ ability to react at any point in time.

Stimuli, Sensitivity and Reactivity: Physiology and pharmacology have clearly defined (1) sub-threshold intensity of stimuli, (2) effective threshold stimulation and (3) ultimate depressing overstimulation with or without damage. These merit re-emphasis because of the continuing tendency to think in non-dynamic terms of processes such as schizophrenia. Thus, observations stressing the high threshold to stimuli and the low reactivity in the chronic schizophrenic may obscure the etiologic possibility that some individuals become schizophrenics precisely because of excessive sensitivity to what would be sub-threshold stimuli for others or because of organ over-reactivity to those stimuli. It is by no means beyond the realm of possibility that greater sensitivity to stimuli may also carry with it a correspondingly greater susceptibility to damage. The persistence and recurrence of high operative destructive dysequilibria (characterized in these formulations as [ACH+]) may eventuate in such damage (latent in the pre-psychotic patient, patent in the psychotic) that the organism loses in sensitivity to stimuli and/or capacity to react.

The existence of sub-threshold, latent or currently undetectable damage to mediating and end-organ elements may characterize the "pre-psychotic". This may be one of the under-

lying differences between the woman with high compensated [ACH+] equilibria going through a normal puerperium, and one breaking down in a psychosis.

Organ Capacity: The functional performance of an organ may be expressed in terms of output, reserve and total capacity.

1. Current organ output, at any one point in time, is the quantity and quality of the organ response to existing stimuli. In the normal, it is usually commensurate with these stimuli, in the abnormal, commonly quantitatively disproportioned or qualitatively inadequate.
2. Current organ reserve is the extent to which an organ can increase its output in response to an endogenous demand or when subjected to additional specific stimuli to which it is sensitive. A measure of reserve is, in no sense, an indication of current output or of total organ capacity. The fact that, at any one point in time, some schizophrenics may have a low adrenal cortical reserve in no way excludes the possibility of a high current cortical output at that point. In fact, one could readily comprehend how persistently high output can impinge upon the reserve. On the other hand, low reserve need not indicate the existence of a high output, for both output and reserve may be low.
3. Organ capacity may be defined as the sum of current output and current reserve.

   These expressions of functional performance are predicated upon three additional factors:

   (a) Prior organ output or the total output of an organ up to the point in time at which it is under study, can, of course, exert a considerable influence on its current total capacity. In some individuals, prolonged function, particularly secretory, may express itself in a relative lowering of capacity. Remissions in schizophrenia could theoretically reflect such a change in the mediating endocrine mechanisms, so that according to the terms of these formulations, [ACH+] dysequilibria may be rectified when protracted adrenal cortical hyperactivity leads to relative "exhaustion" and reduction in output. If the irreversible neuronal damage is not too marked, the patient may enter a spontaneous, clinical remission resembling a recovery.

   (b) Prior organ damage, previously touched upon in the discussion of overstimulation, obviously can influence current organ function—be it endocrine or neurological. Endocrinologically, it may express itself in abnormal reactions to stimuli; neurologically, in quicker break-down following shifts in endo-

crine equilibria. This aspect has already been examined as one of the possible reasons why, of two individuals subjected to the same types of stress, one develops a psychosis, and the other does not.

(c) Organ diathesis has long been the subject of speculation. That it is an ever-present factor need not be challenged, even as one seeks to reduce it to its precise role and divest it of its mythical trimmings. A significant part of the neuronal protein and enzyme system sensitivity, as well as endocrine reactivity and capacity may be inherited. Diathesis may also determine, in a measure, which end-organ —lungs, stomach, skin or colon—will suffer a psychosomatic disorder. In effect, to examine cellular structure and function at any point in time is to view the resultant of current stimuli acting upon tissues endowed with certain inherited characteristics, and significantly modified by a series of developmental experiences and accidents.

For those who contend that "an inheritable constitutional factor" is *the* determinant in schizophrenia, this concept might be expressed in terms of our formulations as follows: the inherited characteristics of an individual's adrenal, pituitary and gonadal organs may be such that they may react in chronic hormonal dysequilibria with consequent prolonged biochemical traumata to neurones predisposed to damage through heredity.

That this does not *automatically* doom all siblings of a schizophrenic to schizophrenia is understandable, since germ plasm need not be similarly inherited among siblings, since intrauterine experiences are not identical, and since the inherited structures are not necessarily subjected to precisely the same familial and environmental viscissitudes from preconception on through the life situation. Furthermore, siblings, even under similar stresses, may be able to maintain hormonal equilibria and prevent the development of a psychosis.

Susceptibility to Psychoses:

(a) Congenital Predisposition: the problem of heredity in schizophrenia and certain other psychiatric disorders may be complicated by intrauterine hormonal factors. Theoretically, a child may, through chance, escape hereditary pre-disposition only to be exposed to the effects of maternal hormonal dysequilibria upon its neuronal and endocrine structures and functions.

(b) Can the schizophrenic or other psychotic processes be initiated or reproduced biochemically? Some might be tempted to indulge in the wish-fulfilling fantasy of a mythical person with neuronal structure so resistive, and compensating mechanisms so potent that dynamic

equilibria could be maintained within a range sufficiently close to normal that his remarkable neurone structure is preserved despite the most outrageous traumata. Epistomologically, it would serve the purposes of medicine and humanity better not to assume, since we can only assume, the dominance of uninfluenceable constitutional characteristics, for it could become the root of investigative and therapeutic defeatism.

Today, certain aspects of this theoretical problem have acquired practical importance with the advent of ACTH, and cortisone. With the dosage ranges currently in use, on the basis of these formulations, one would anticipate benefits in some subjects and the precipitation of a psychosis in others.

Benefits with ACTH should accrue in psychoneurotics whose adrenal cortices are responsive and have adequate reserves. Symptomatic improvement in similarly predisposed psychosomatic, and certain depressed patients could likewise be anticipated. ACTH given in large enough amounts over a significant period of time to pre-psychotic patients and psychotics in remission, who have responsive adrenals with good cortical reserves, would, according to these theories, precipitate an active psychosis.

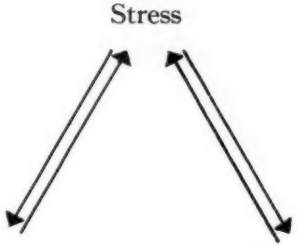
Cortisone, on the other hand, may hypothetically benefit psychoneurotics, psychosomatic, and manic-depressive depressed patients, but precipitate psychoses in certain pre-psychotics and psychotics in remission—irrespective of the status of their cortical reserve.

Theoretically, therefore, the administration of ACTH (in the presence of extensive cortical reserves) or cortisone may eventuate in a significant incidence of psychoses. This undesirable side-effect is hypothetically preventable and reversible according to the formulations presented.

It follows that in ACTH and cortisone therapy, not only are dosage levels and duration of therapy matters of concern, but of equal importance is the considerable incidence of pre-psychotic and mildly psychotic disorders in the general population. Consideration of ACTH and cortisone therapy, therefore, makes mandatory a most thorough psychiatric examination and endocrinologic evaluation of each individual patient, before any decision can be reached as to their use.

The Organism and Its Environment: The organism functions in relation to an external and an internal environment. At all times, the internal environment is integrating within itself, elements from the external environment, even as it exerts its own influence upon the external environment. In the biochemistry of the body and in the personality and mental status of the individual, we find the ultimate results of the interaction between the two.

Some of the trigger mechanisms of both internal and external environment activating the endocrine dysequilibria in the disturbances we have discussed, are fairly well-known. The recognized stresses are integrated within our formulations as trigger mechanisms participating in the precipitation and development of psychiatric disorders. Of primary concern to our postulates, however, are the neuroendocrine mediating mechanisms through which the stresses exert their effects, and the end-organs upon which they act, such as the neurone—in the psychoses and psychoneuroses—and the respiratory and gastrointestinal tracts —in the psychosomatic disorders.



For a considerable time, intensive interest and investigation have centered in the stresses—psychic, social and somatic.

A. Psychic Stress and Trauma:

1. Endogenous Psychic Stress (EnS) refers to a complex of many stresses, one of which is the familiar internal conflict of psychoanalysis. Its psychodynamics are accepted, its relationship to the psychopathology of the psychoneurotic symptom picture is well-defined and its therapeutic manipulation is an established psychiatric technique. Much remains to be done in the application of psychoanalytic precepts to the prevention of emotional disorders, in the extension of psychoanalytic principles to non-psychoanalytic therapy, and more fundamentally, in the further clarification of the biochemical mechanisms whereby internal conflict and other stresses exert their effects upon neuronal structure and function.
2. Exogenous Psychic Stress (ExS) has long been recognized to exert its influence upon emotional development and disorders of the personality. The social structure of the environment, as exemplified by the family and society, make a continual contribution to the development of psychiatric disorders, through their familial, social, educational, economic and military pressures. It is in the manipulation of some of the exogenous stresses and in the alterations of the patient's personality in reaction to

these, that the non-psychoanalytic therapies seek to make their contributions.

B. Physical Stress or Somatic Trauma:

For purposes of simplification, physical stress is referred to as (PxS) even though physical stress, like psychic stress, has endogenous and exogenous components.

1. Endogenous Physical Stress may be presented in terms of a few of its typical representatives among the bodily illnesses; such as, hypertension, cerebral arteriosclerosis, intracranial tumor and anoxia of severe anemias. In the last analysis, the endocrine dysequilibria resulting from exogenous and endogenous psychic stress, exert their influence in chemical and physical trauma to the neurone.
2. Exogenous Physical Stress may be exemplified microbiologically, by the Treponema pallidum and the meningococcus, chemically, by such poisons as alcohol and carbon monoxide and physically, by such direct trauma as concussion, cerebral laceration and the intracranial bleeding of skull fracture.

At this time, it would be well to examine a little more fully the expression "neuronal damage" in relation to certain psychoses. Assuming that all neurones are simultaneously exposed to the same endocrine trauma and recognizing the diffusibility of the essential elements involved, the diffuseness of the resultant damage is readily appreciated. In view of the diffuseness, the graded regional (as distinguished from focal) character of the damage, then challenges explanation. It should not be surprising that almost all of the damage is evident in cerebration rather than in the sensory, motor or still more vital areas. Here again, the different vulnerability of the various areas reveals the phylogenetic character of the evolution of our defense mechanisms and over-all development. Since, phylogenetically, thinking is the most recently developed, and the least vital, function, it is impaired first. The sequence of vulnerability and, therefore, of probable damage is commonly encountered in the acute effects of alcohol and other pharmacologic narcotics. This order of events which has been related to susceptibility to damage may reflect the order of sensitivity of regional neurones.

THE IMPLICATIONS OF THESE FORMULATIONS

The implications of these formulations cut across the arbitrary boundaries of our specialties, beyond psychiatry, endocrinology, obstetrics, surgery and internal medicine, into the basic sciences. While they have evolved out of clinical and experimental psychiatric considerations, it will be seen in subsequent sections, that they may make significant contributions to

a better understanding and management of diabetes, severe burns, peptic ulcer, allergies, and of such problems as hyperthyroidism. These formulations may offer new perspectives on many clinical and experimental findings.

Summary

Some fundamental concepts of physiodynamics, and the clinical and experimental considerations out of which they evolved, have been presented; many basic physiologic premises have been restated; some have been amplified, and a few new concepts were introduced. A number of psychiatric observations and analyses have been set forth and integrated within a single and encompassing theoretical frame of reference.

In an application of the antidyne concept, histamine has been presented as a vital physiologic substance—as a hormone. The possible biochemical effects of the mediating hormonal mechanisms relating stress situations to their ultimate effect upon neuronal structure have been examined. Triggering stress situations have been briefly reviewed. All of these considerations have been referred to specific psychiatric situations.

Experimental and clinical experiences have been related to the theories and have been examined within the context of the new postulates. The theoretical basis for the favorable response of a few involutional psychotics to high steroid therapy has been explored. Factors which may account for the differences in progression, "scarring", and ultimate prognosis in different forms of schizophrenia and manic-depressive psychoses have been posed. Reasons for the comparatively easy control of postpartum and involutional psychoses have been discussed. Some contrasting aspects of psychoneurosis and psychosis, of postpartum psychosis and asthenia have been examined. An etiologic consideration in the development of pubertal, or adolescent, schizophrenia and its probable susceptibility to treatment, have been presented and the role of diathesis has been briefly discussed. A number of hypothetical and practical considerations, raised by the advent of ACTH and cortisone and their beneficial as well as their psychosis-precipitating potentialities, have been theoretically approached. The implications of the formulations for other branches of clinical medicine have been intimated.

This report has thus presented some new formulations in what has been termed physiodynamics, and has related these to a number of medical problems, primarily psychiatric.

Due to space limitations, bibliographic references will be included in the concluding sections.

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THE PSYCHIATRIST LOOKS AT CONTEMPORARY ALCOHOLISM*

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Although most workers in the field of alcoholism feel definitely that alcohol by itself does not produce alcoholism, nevertheless, it should certainly be kept in mind that alcohol is not an inert substance—like water. Pharmacologically, alcohol (at various stages of its effect on the human—and animal—organism) can act as a sedative, hypnotic, analgesic, narcotic, temporary anesthetic, and, in some cases, as a permanent anesthetic, producing death. The uses of alcohol as a relaxer and pain-killer are quite familiar.

Traditions and ceremonies of various types incorporate the use of alcoholic beverages.

Again, in regard to crime, one must keep in mind the following:

1. Crime is often planned in a place where alcohol is sold.
2. The tavern is the place where the criminal seeks his accomplices.
3. The criminal is seldom courageous and uses alcohol to depress his inhibitions and allay his fears.
4. The spoils of crime are divided often in the tavern.
5. Alcohol removes the element of self-criticism from the criminal in relation to himself and his acts.

It should also be kept in mind, as the following material is presented, that we are here attempting to give an inclusive survey of present-day scientific and factual concepts about this serious, and increasing, health problem. Such a survey requires the use of generalizations which concede the existence of qualifying exceptions.

In a practical, scientific-approach survey, one is neither "damp, dry, nor wet" but considers the goal of sound health—physical and psychological—which is a basic imperative for us all in these days of turmoil and responsibility.

The fact that alcoholism is now the subject for medical meeting discussion, civic forums, and industrial conferences, in contrast to ten years or so ago when this problem was not even touched upon in many medical schools, much less recognized by most leaders, or under research investigation, is a fact that is heartening and disheartening.

We would all be pleased if this behavior illness problem were not so prevalent in our contemporary society. Its ravages

*Read, in part, at the Industrial Conference on Alcoholism March 23, 1948, held at Chicago, Illinois.

are worse and more varied than those of any other specific known medical or psychiatric sickness. The toll it takes each year in lives, due to alcoholically induced accidents; in happiness, due to marital and family life upheavals produced or increased by alcohol consumption; and in actual cash, from the home budget to State and Federal funds is a toll greater than we can calculate, for the intangible serious aspects of alcoholism—the symptom of illness—are at least as many as the tangible ones.

On the asset side of the definite increased awareness of and organized interest in alcoholism, are the facts that today nearly all recognize that there is a difference between "social drinking" (even when hangovers are involved) and alcoholism; that the alcoholic is a sick person, not just a "bad actor," and that alcoholics as a class are no longer classifiable as "bums" and "drunks." Many of our most intelligent, versatile and useful citizens have alcohol problems. They are, medically speaking, alcoholics, and require treatment for the underlying causations and to learn how to live without ever again using this socially acceptable, ever-present beverage, and also to learn how to live in more satisfactory harmony with themselves and others. The nervous irritable qualities of temperament that, aside from any psychiatric illness, so often underlie the drinking pattern have to be changed into calmer and more tolerantly mature acceptance of distasteful facts. Treatment, by whatever method, essentially consists in this achievement: of helping an individual change (or strengthen) his personal reactions to the world he lives in and to other people, and never again touch alcohol in any form.

Now, when we use the terms "social drinking" and "alcoholism," what is meant? Medically, an individual is considered to be an alcoholic if his use of alcohol interferes with one or more of his important life activities, as for example, his job standing and ability, his reputation, his home-life. This interference is shown in behavior, in his inability to stop drinking at will, in the fact that alcohol "handles" him; promises, resolutions, even threats are powerless against this domination. In contrast, the social drinker can stop drinking at will. He limits himself to several drinks, except at parties and even then usually stops short of actually getting drunk to the extent of not knowing what he is doing. The social drinker may, frequently, be injudicious in speech or action, but does not so lose self-critical judgment as to be involved in real jams, fights with strangers, police, and so on.

However, *heavy* social drinkers—and their numbers appear to be increasing—*do* get themselves and others into difficulties; and this group constitutes a danger as an accident risk; also, from their ranks, the chronic alcoholic usually develops. Heavy social drinking, as such, from the medical point of view is, today, more and more a problem and should be dealt with through education and other measures. It does not, however, constitute alcoholism;

although I, for one, certainly feel it can factually be called *incipient* alcoholism; that it should never be dismissed lightly; and that all precautions possible should be instituted to halt and eradicate it whenever it is known or suspected. Many business leaders, professional men, and high powered executives would be found to be in this medical bracket. With the present world and national stresses subjecting us all to unusual nervous and emotional strain, such individuals are playing with dynamite as they drink their distinguished concoctions.

Further, I personally am convinced that heavy social drinkers actually cause more trouble, as a group—and this group numbers into the millions—than do the estimated ¾'s of a million alcoholics. The reasons for this personal conviction are based on some 20 odd years' experience in psychiatry and of observing the social climate of "our times." One need not go far for evidence. At any hotel bar or grill you may see at any dining hour a number of well-dressed, presumably influential men who, as the rounds pile up, become louder, more argumentative and expansive in movement. When calm judgment in business or profession is required, alcoholic states of mind are comparable to a cut-off in electricity at the peak hour of production.

I am certainly opposed to prohibitionary measures, for they are opposed to the working of human nature and never produce any but poor to bad results. The solution for this heavy social drinking—in which, also, many, many women are participating and which, I believe, relatively few people recognize as a dangerous hazard—might be found in the building of social attitudes against behavior that is inappropriate, stupid, and harmful to others. The drunken driver and the drinking driver are potential killers.

Heavy social drinking, especially in the daytime, produces inefficiency. The executive whose bourbonized judgment dictates a business corporation letter and thereby loses several millions of the stockholders' investments, hurts and harms in a bloodless way. The clerk who, following the patterns set by his so-called superiors, also drinks at the noon-hour and makes typographical or other errors the rest of the day may, as a consequence, be fired. Or, he may mix things up so much that weeks are needed to untangle the matter, causing more work for others, and costing his company many dollars.

Such episodes of "absenteeism-on-the-spot," from the top down, are probably as many as, perhaps more than, those of orthodox absenteeism due to alcoholism.

If, through various opinion-molding media, we could change the prevailing social attitude about heavy social drinking and especially about daytime drinking so that instead of it being considered obligatory, or "smart," even the waiter would look astonished and disapproving, we should all be saved much

trouble, and so far as auto accidents alone, are concerned, much tragedy. And I do not think the liquor industry would suffer great financial losses. They too have the same problems of inefficiency, alcoholic errors of precision and absenteeism due to alcohol. So much for social and heavy social drinking.

We have already medically defined an alcoholic as one whose drinking handles him and seriously interferes with his important life activities. But how did he reach such a stage—and what makes an alcoholic? We all know drinking people, even heavy social drinkers, whom we cannot call alcoholics. On the other hand, frequently we treat a patient for an alcohol problem whom the world would never consider an alcoholic, expecting from that term, fireworks and obvious dissipation such as Ray Milland portrayed in "The Lost Weekend." Many a mild-mannered, immaculately groomed man, and woman, highly respected, comes under psychiatric care for alcoholism, who outwardly looks no different from any other—I use quotation marks—"Normal" person. These individuals are certainly the hardest to treat and may be called the worst type of alcoholic because theirs is an insidious, unseen, quiet, almost cancer-like form of drinking. Public opinion is not against them. Their own insight is very poor. They don't do anything "bad." Unless propped, propelled, and pushed by some unswerving relative, this type of drinker continues at large until maybe years pass before, like the one-hoss shay, he falls apart and his actual condition of alcoholism can be recognized. It is then, often, too late to do much, for irreversible organic brain changes have taken place.

In general, one may sum up the making of an alcoholic by the following:

He is a product of his ancestry, the way his grandparents and parents lived, the extent of their drinking, their racial background; of his personal early experiences in life, the inevitable clashes with other personalities, the likes and dislikes the disciplines, the heartaches of childhood and how he assimilated or did not assimilate them; of, also, later experiences in life, from job changes to marriage or love experiences; of religion or lack of religion and basic belief, vague or less vague philosophy; of the social drinking habits of his friends; and of the social pressure to drink occasioned by those habits. This "pressure" is far more prevalent in some lines of work than in others. The average technician, for example, does not have to contend with the demands to "take" a drink that a salesman, especially of industrial commodities, does.

Alcoholism as a psychiatric illness-symptom presents itself like the top of an iceberg. The submerged unseen part is what we have to get a clear understanding of. It's not enough to say, "Don't take any more." Or, "I won't drink any more." The alcoholic, produced by all these factors just enumerated, in

varying quantitative and qualitative amounts, is a very sick person whose drinking results from all the inner turmoil and/or rebellion which he attempts to allay and narcotize by alcohol, for him, a drug. Once the alcohol is taken away, the underneath part of the iceberg has to be explored and fluoroscoped and dissected and enucleated and treated, if you will pardon this mixture of clinical terms. In fact, the alcoholic himself, is a mixture of clinical terms. In part he is manic-depressive; in part, schizoid; in part, paranoid; in part, given to emotional outbursts resembling an epileptic equivalent. He is definitely neurotic; and, to the extent that so far as the seriousness of his drinking is concerned, his judgment is nil and insight poor, he is "psychotic." Small wonder that he has always been a thorn in the side of the medical profession. Even today, with all our vaunted knowledge about him and techniques of treatment, with all our clinics, "work-ups," lay groups and hospital arrangements, certain alcoholics can still be a source of trouble and confusion, equalled only by the 100% psychopath.

Because alcoholism is symptomatic of so many varied personality and behavior disorders, psychiatrists are becoming more and more interested in this serious problem.

The medical definition of an alcoholic—as distinguished from the social drinker—is one whose drinking harmfully and definitely interferes with one or more of his important life activities. He may lose time from work due to drinking, or the quality of his work may suffer, or his home-life harmony may be disrupted, or he may so speak and generally conduct himself that his reputation and relationships with others suffer. In spite of evidence, clear to other people, that he is having difficulty with alcohol, he himself usually does not recognize the seriousness of the situation, partly because of the prevailing social attitude that having a drink or two is a usual pleasant custom, an attitude that he has absorbed and that constitutes a form of "social pressure" until he can reach the place—if his brain is intact and his thinking straight—of admitting that just as the diabetic cannot handle sugar, so he cannot handle alcohol without adverse results.

Now, there are many types of alcoholics, and the need for careful discrimination is important both for actual treatment and placement and for a scientific application of the medical statement that alcoholics are sick people. In previous times, those with an alcohol addiction were usually considered as a group to be "hopeless drunks and bums." This attitude still exists in many sections and circles. However, we know it is not accurate, that not all with an alcohol problem are "hopeless" and that many persons with this problem have high intelligence, fine, delicate make-ups and are among our community and social leaders. In the same way, in stating that "alcoholics are sick people" we must break down the generalization. To be of aid to the individual

and family, one must first understand that alcoholism is symptomatic of psychopathology—disorder or illness in the personality functioning, that the pathology may be primary, or secondary, that physical complications may be in the picture (organic brain damage or deterioration, etc.) and that in order to attempt to treat the patient we must know about his personality make-up, presence of any major psychiatric illness, of any minor psychiatric illness, and about his actual life-setting and circumstances.

Pharmacologically, alcohol depresses the "higher" brain centers, impairing or removing temporarily the brake-power of judgment, discretion, and control. Thus primitive impulses and emotions are set free. Actually, alcohol does not make one "tight"; it makes one "loose."

There are individual differences in so-called "tolerance"—ability to drink without subjective or objective behavior, motor, or other changes; differences also for the same individual, depending on the amount of food in the stomach, emotional situations, fatigue elements, sugar metabolism, and so on; and there are different individual reactions to various alcoholic beverages.

In general, when alcohol is ingested it produces the following physiological changes in functioning:

> Poorer co-ordination of thought and body action; diminished acuteness of sensory perception; delayed or weaker motor performance; more frequent errors in precision work; diminished physical efficiency.

Pathology of Alcoholism

Formerly, alcohol was thought to cause definite heart trouble, kidney damage, and various other organic pathology. There has been little scientific evidence to substantiate these views. Aside from temporary symptoms resulting from an acute drinking bout, such as a thick-coated tongue, bloodshot eyes, and a gastritis of varying degrees, most of the pathology, as such, is found in disorders in the neuropsychiatric field. Occasionally, cirrhosis of the liver is found, which is associated with depletion in vitamin content, but it is also reported found in as many non-drinkers. Neuropsychiatric disorders include: encephalopathies of various types, neuropathies, and behavior disturbances (psychopathology), evidenced by personality, emotional, or mental deviations from the individual's usual behavior or that commonly accepted as usual by society.

Psychopathology

The following are types of reactions in which alcohol plays a very important part in producing the clinical picture, in most cases these are associated with vitamin deficiencies because of inadequate food intake while drinking:

1. Acute intoxication with excitement;
2. Acute intoxication with stupor;
3. Acute intoxication with convulsions;
4. Delirium tremens;
5. Acute and chronic hallucinosis,
6. Mental deterioration and dilapidation;
7. Korsakow's psychosis;
8. Personality and ethical deteriorations;
9. Chronic depressive reactions;
10. Paranoid developments.

PSYCHODYNAMICS

Since alcoholism is a symptom of a personality illness, an emotional illness, or a more serious psychiatric illness or disorder, one attempts through careful examination to uncover the causes and/or psychodynamics producing this symptom, which may be evidence of primary psychopathology or of secondary psychopathology. For purposes of convenience, we can summarize these as follows:

1. As an escape from painful life-situations;
2. As an attempt to escape from one's self-evidence of maladjusted personalities;
3. As a combination of these two;
4. Evidence of neurosis;
5. Evidence of psychosis;
6. Evidence of feeblemindedness;
7. Evidence of psychopathic personalities;
8. Evidence of some epileptic conditions;
9. As a result of heavy social drinking, habit, time body changes and strains of life;
10. As an escape from incurable physical illness.

The individual "psychodynamics" of why people drink is a question now productive of so many answers that the whole issue of treatment including prevention has become rather obscured. Individual motivations for excessive drinking may be summarized as follows:

1. A self-pampering tendency, which reveals itself in a refusal to tolerate, even briefly, any unpleasant state of mind—boredom, sorrow, anger, disappointment, worry, depression, dissatisfaction, and feelings of inferiority and inadequacy. A childish demand for "I want what I want when I want it because I want it," perhaps expresses the attitude of many alcoholics toward life.
2. An instinctive urge for self-expression without the determination or staying powers to organize this urge into creative productive action.

3. A more than usual craving for emotional experience which calls for the removal of intellectual restraint.
4. Powerful hidden ambitions without the necessary resolve to take practical steps to attain them, with resultant discontent, irritability, depression, disgruntledness, and general restlessness.
5. A tendency to flinch from the worries and responsibilities of life and to seek escape from reality by the easiest available means.
6. An unreasoning demand for constant happiness or excitement.

To repeat, alcoholism is felt to be evidence of an escape from reality; or of a maladjusted personality; or of latent or overt homosexuality; or of intense unconscious and self-destructive tendencies. We feel that any one of these interpretive conclusions verifies the presence of anxiety, hostility and/or tension; and psychiatric probing by various methods may bring out as their cause:

1. Some early traumatic event.
2. Disturbing experiences at certain periods of life which the individual's personality was unable properly or satisfactorily to assimilate.
3. Identification and imitation factors, rather than any inherited disposition towards alcoholism.
4. Conflicts causing "pent-up" charges which require narcotizing either the anxiety itself or the anxiety-controls.

So far as treatment is concerned, first, it is quite obvious—even to the non-medically, non-psychiatrically trained "average person" that many alcoholics have been able to stop drinking via many so-called approaches. Some stop by themselves, unaccountably, or "for some reason or another;" others stop because of a religious experience or conversion; others by and with the aid of social workers. Some stop drinking with help from lay therapists; some, from lay groups; and others, from lay-and-religious groups, if one may use the term, such as, for example, The Salvation Army.

Even the old "Keeley Cure" helped many alcoholics and some are now advocating a conditioning treatment without psychotherapy; while many, with deeper interest, use the conditioning, or aversion, treatment in order to get a beachhead on the patient and then follow up with psychotherapy.

Psychoanalysis alone, hypnosis alone and hypnoanalysis alone have all been quite unsuccessful.

From the medical, psychological and psychiatric point of view of treatment, each individual presents an individual problem and must be handled as such. However, in general, the methodology can be described as follows:

First of all, one wishes to determine what type of psychiatric

problem one has to deal with; how much deterioration is present; how serious is the extent of the drinking; whether the individual really wants help.

Remembering that a man or woman with an alcohol problem may come or be brought in any stage from that of acute D.T.'s to that of the remorseful hangover period, and that the sources of referral may range from the jail to the president of the company (or the president's wife), one should deal practically with the problem at the time. The method of selection follows the general lines enumerated below:

1. The individual who desires to abstain but who is unable to do so by himself. This patient has good intelligence, some maturity in his make-up, and his life habits and contacts indicate stability. This type is to be handled by extra-mural or office therapy of regular, frequent visits which are the patient's responsibility to keep, and sedation as indicated.
2. The individual who desires to abstain but who is unable to do so by himself. This patient has good intelligence, some maturity in his make-up, but his life habits and contacts are poor. He should, therefore, be placed in a non-institutionalized farm arrangement, where psychotherapy, including help and guidance away from his contacts, is started.
3. The individual with good intelligence and rather immature make-up who should abstain but does not desire to do so. Most in this group have poor habits and contacts, although some do not. This type should be placed on an alcohol farm, sanitarium, or hospital under the Inebriate Act, for a definite period of time.
4. Korsakoff's psychosis and alcoholic deteriorated patients should be treated in mental hospitals permanently.
5. Individuals with delirium tremens and acute hallucinosis should be handled and detoxified in the office equipped and prepared to do so, or placed in psychopathic hospitals and then studied in the way described for proper handling.
6. Feeble-minded individuals with a history of repeated arrests, commitment to the workhouse or house of correction should, after careful examination, be handled by the penal system.
7. Chronic alcoholics should not, of course, be treated in general hospitals, which are not equipped to handle this problem, where treatment is usually mere desaturation and discharge at a time when the individual is psychologically demobilized and ready for another bout. This pattern of acute intoxication, brief desaturation periop and resumption of drinking, is easily established and leads

with more or less rapidity to involvement of the central nervous system. It is felt that this type of superficial therapy has contributed to a great deal of the fatalistic attitude of some lay and medical groups about treatment of alcoholics in general, and to the feeling that "all drunks are hopeless."

This method of selection is based on data obtained from the patient and/or members of his family, social service or other agencies. As in any psychiatric examination, one needs to know all the important life details and facts. With the non-intoxicated, non-deteriorated patient, who may be interviewed in the office, or at the hospital after he has cleared up from the effects of drinking, a complete history is taken from birth to the present. This should include the patient's place in the family group; developmental data; the presence or absence of disturbing behavior or situations in childhood, adjustment to school, vocational record, marital status, sexual activities and attitudes, religious habits and feelings, financial status, family situations, general health throughout life (including details of major illnesses or operations or accidents), and a close survey of the present life situations and persons involved.

A psychiatric examination should include formal mental status of general behavior and habits, activities, mood, special preoccupations, sensorium and intellectual resources, and insight. To determine the presence of any organic pathology, a physical and especially a neurological examination should be made, with specific laboratory tests as indicated. A member of the family, or close friend, should be interviewed in order to obtain objective data about the drinking problem, drinking behavior, and general personality of the individual, with emphasis on his assets and good qualities as much as on the difficulties his drinking has caused. (The examination should also include personality depth-studies through use of the Rorschach analysis or the Murray Thematic Apperception Test. The sensorium and intellectual resources are further tested by the Kohs' Blocks test, the Wechsler-Bellevue Adult Intelligence Scale, Electroencephalograms, and other tests as indicated).

Based on all these findings, one should prepare a more or less detailed summary of the patient's assets and liabilities to aid in understanding and medically treating him as an individual. A similar examination-interview with the mate is extremely important to help find out how great a part, if any, the friction of personalities has played in contributing to the production of strains or out-and-out irritants that the individual sought escape from via drinking.

Treatment

No one who has had an alcohol problem can ever again

drink "socially." Science does not yet know exactly why this is so—what change has taken place in cell tissue but pragmatic experience has proved beyond doubt that once a person's drinking has crossed the line onto pathological drinking, he can never "handle alcohol" again. He can reintegrate his personality and often achieve more even than in the early, "social drinking" days; but he must be a total, permanent, forever-after abstainer.

These facts must be bluntly stated at the outset, and accepted by the patient if desired results are to be expected. Frequently it is possible to modify poor vocational adjustment, or irritating martail situations involving sexual incompatibilities, parental conflict over the management of children, etc. The patient himself may not be conscious of the strains of all these things upon him. When it is not possible to modify the situation, it is often possible to change the patient's attitude toward the difficulties he has to meet. Many a person becomes morbidly self-accusatory and fatalistic because of what he considers his failure to modify the unmodifiable. Such an individual may be greatly helped by mutual discussion, constructive criticism and wise guidance.

The goal of treatment therefore is to teach the individual who can be helped, to learn how to live without ever again using alcohol in any form.

This involves usually a rather lengthy rehabilitation period of habit-training, re-directions in life, and helping the patient to learn intellectual control over mood (emotional) domination. Individual therapeutic interviews utilizing the principles of ventilations and desensitization on a distributive analytic basis help give the individual a chance to let off steam and react less strenuously to previous upsetting situations or conflicts, and also give him insight into some of his modifiable drives and attitudes that cause him difficulty. He is indirectly taught to accept tolerantly and maturely other people's personalities without feeling unnecessarily "blocked" or frustrated, and a careful appraisal of his personality liabilities and assets helps him to reorganize his views and values and goals and capacities along more constructive, satisfyingly productive lines.

We must always remember that while many individuals drink to relieve various feelings of discomfort or psychic pain, others drink as part of a more serious psychiatric picture involving mood-swings or schizophrenic features, etc. The need of thorough examination, and understanding of the underlying personality illness or disorder cannot be over-emphasized.

For all these reasons, interviews with the husband or wife or family members assume major therapeutic importance. Many a poor result of treatment is attributable to lack of any insight whatever on the part of those closest to the patient; they too must

learn to accept unmodifiable facts of life and to utilize principles of emotional hygiene in their interpersonal relationships.

Success in Treatment

Experience with alcoholic patients indicates that successful results are accomplished by the following factors:

1. Careful selection of patients: that is, those who desire to learn how to stop drinking, who have average or better intelligence, some level of emotional maturity, undamaged brains, with place of treatment depending on their business, home, social contacts, etc.
2. Personality of the psychiatrist, who should be plastic, sympathetic, tolerant, but firm. (Ideally it is important for the psychiatrist and staff-members to be total abstainers).
3. Distributive analysis and psychotherapy with personality discipline, re-education, desenitization and ventilation.
4. Adjunctive vitamin and/or insulin therapy in controlled dosage, to aid in the biochemical functioning.
5. Interpersonal relationship of patient and therapist.
6. Suggestive influences, including community and civic activities.
7. Interviews with the mate or family members.
8. Full co-operation of the patient and his associates.
9. Intensive follow-up for a period of many weeks, and continuous follow-up for life, by means of correspondence, phone calls, annual visits, etc.

Prevention

On a broader basis, alcoholism now constitutes a major national health problem, all workers in public health and welfare agreeing that all too frequently alcoholism is one of the outstanding factors in the production of serious difficulties for individuals and the community. As one example, many a juvenile delinquent comes from a home broken up by the effects of alcoholism.

The need for preventive education and understanding is great. Recently much more attention has been focussed on the problem of the alcoholic individual and in many states and cities, committees have formed to handle or attempt to handle this problem. Because the serious implications of alcoholism lie in the field of behavior, medical psychiatric supervision is needed to properly guide individuals and groups desirous of "doing something about" alcoholism.

It is important to keep away as much as possible from emotional, political, or other attitudes that might obscure the clear fact that treatment of the alcoholic himself is primarily a

medical rather than a moral problem. Wise preventive education should consist of recognizing that, in general, excessive dependent drinking is a frequent result of poor unsatisfactory emotional and other life-habits apparently associated with some of the contemporary social pressures of speed, noise, change and general insecurity in nearly all spheres of life. The use of alcoholic beverages is traditional in most parts of the world and previous attempts at regulation have failed to get at the root of the problem because it is inherent with the individual himself, his personality, and the specific life-setting with all its frustrations, frictions, etc., in which he finds himself.

We feel, therefore, that information centers where problems of alcoholism could be referred, associated with treatment facilities to handle acute problems (a psychiatric hospital or unit) and adequately staffed with trained personnel (psychologists, nurses, social service workers) under the supervision of a psychiatrist offer the most practical working program for the community and the individual. Affiliated services would include farms where selected patients could receive psychotherapy and common-sense re-education in life; and protective institutional arrangements for the more seriously psychiatric types, including the feebleminded and psychopaths—the latter constituting, of course, the most difficult rehabilitation problem.

In conclusion, alcoholism is a serious national health problem and it is also a social problem requiring new and different social attitudes about excessive uncontrolled drinking. The alcoholic is a sick person who needs competent proper medical and psychiatric care, treatment, and follow-up supervision. The only possible goal for the alcoholic lies in his never again taking a drink. The only possible goal of treatment, along whatever lines, therefore, is the well known fact of total permanent abstinence for the ex-alcoholic. The ex-alcoholic should not be made to feel, either in the home or community, that his illness was a crime. He should be given every possible proof of moral support in maintaining his health and the same sort of consideration—no more and no less—that an ex-T.B. patient receives.

To aid in the prevention of alcoholism, greater stress on sound physical and mental health habits and on the emotionally important elements of family and religious life, with lessened pressures of speed and dollar-sign success would, we feel, help decrease the production of many emotionally immature, early neurotic, early psychotic, and incipient alcoholic personalities. One need not enumerate today, the terrific sociological pressures upon every one of us, and the consequent need to maintain health in all ways.

From the practical standpoint, prevention and treatment, both, would be best organized and instituted to serve the community through:

1. Information centers (similar to those maintained by our T.B., Cancer, Rheumatic Heart Associations) where material could be obtained by the public and through which contacts with medical and psychiatric set-ups could be made.
2. Through factual courses on alcoholism, its treatment and prevention, given in all our medical, nursing, and social service schools.
3. A hospital or section of it in every state where patients with alcohol problems could be properly treated and given the medical-psychological service they require.
4. State Hospital set-ups for the treatment of some alcohol patients.
5. State Farms where physical rehabilitation and social psychiatric help under the supervisions of a psychiatrist would be available.
6. Extra-Mural Clinic centers, located near the alcohol hospital or information center, to serve as a diagnostic unit, treatment unit, social service unit, and training unit for workers in this field of behavior illness.
7. A concerted program of education against *heavy* social drinking, beamed at the reading and listening public—including the teen and twenty agers—and supported as a Public Health Service.